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(54) **Use of beta blocker for the manufacture of a medicament for the treatment of hemangiomas**

(57) The present invention relates the use of a beta blocker for the manufacture of a medicament for the treatment of hemangiomas, for example of infantile hemangiomas. The beta blocker may be a non-selective beta-blocker, for example propranolol. The present invention

provides an alternative to the known compounds, e.g. corticosteroids, interferon or vincristine, generally used for the treatment of hemangiomas.

EP 2 050 441 A1

Description

Technical field

[0001] The present invention relates the use of a beta-blocker for the manufacture of a medicament for the treatment of hemangiomas, for example of infantile hemangiomas.

[0002] Also disclosed is a method for the treatment of hemangiomas by using the present invention.

[0003] In the following text, the bracketed bolded references are references attached to the cited documents and publication also listed in the reference list after the « Example » part of the specification.

Prior art

[0004] Infantile capillary hemangiomas (IH) Hemangiomas in children are most commonly recognized in the skin and liver. IH Infantile capillary hemangiomas (IH) are the most common soft tissue tumours of infancy, occurring in 4 to 10% of children under 1 year of age as disclosed in Frieden IJ et al, "Infantile hemangiomas: current knowledge, future directions, Proceedings of a research workshop on infantile hemangiomas", *Pediatr Dermatol* 2005; 22:383-406 **[1]**.

[0005] IH is made of a complex mixture of cell types including a majority of endothelial cells, associated with pericytes, dendritic cells and mast cells. Endothelial cells derived from proliferating hemangiomas are clonal in origin as disclosed in document **[1]** and by Bielenberg D.R. et al, "Progressive growth of infantile cutaneous hemangiomas is directly correlated with hyperplasia and angiogenesis of adjacent epidermis and inversely correlated with expression of the endogenous angiogenesis inhibitor", *INF-beta. Int. J. Oncol.*; 14:401-408 **[10]**, Boye E, et al. Clonality and altered behaviour of endothelial cells from hemangiomas. *J Clin Invest* 2001;107:745-52 **[9]** suggesting that hemangiomas arise from the clonal expansion of an endothelial precursor cell, which might be derived of a haematopoietic stem cell as disclosed in **[1]**.

[0006] IH endothelial cells exhibit a distinctive molecular phenotype characterized by immuno-histochemical positivity in document **[1]**: indoleamine 2,3-dioxygenase (IDO) and LYVE-1 both positive in early phase IH and lost during maturation to a blood vascular phenotype, Glucose transporter 1 (Glut-1), Lewis Y Ag (Le Y), FcRγ, merosin, CCR6, and CD 15.

[0007] Regulators of IH growth and involution are still poor understood, but it has been demonstrated that during their growth phase, two major pro-angiogenic factors are involved: basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) which are present in situ, but also in blood and urines as disclosed in document **[1]**. and in Mancini A.J. et al, "Proliferation and apoptosis within juvenile capillary hemangiomas", *A.m. J. Dermatopathol.* 1996; 18:505-514 **[11]**.

[0008] In addition, in situ hybridization for the VEGF

receptor (VEGF-R) in proliferative IH has shown that VEGF-Rs are evenly spread throughout the hemangioma and not yet assembled into blood vessels.

[0009] During the growth phase of IH, histological studies have showed that both endothelial and interstitial cells are in proliferative state (MIB1 staining strongly positive) as disclosed in Mancini et al. Proliferation and apoptosis within juvenile capillary hemangiomas. *Am J Dermatopathol* 1996;18:505-14 **[10]**. and on the other hand during the involution phase the cells exhibit markers of apoptosis as disclosed in **[10]** and Razon M.J. et al, "Increased apoptosis coincides with onset of involution in infantile hemangioma", *Microcirculation* 1998; 5:189-195 **[11]** One hypothesis to explain endothelial cell apoptosis in capillary hemangiomas is the expression of ICAM-1 on the cell surface, but an alternative possibility may be the loss of stimulatory factors such as VEGF **[1]**.

[0010] The adrenergic system is the major regulator of cardiac and vascular function. Capillary endothelial cells express beta 2-adrenergic receptors as disclosed in D'Angelo G. et al, "cAMP-dependant protein kinase inhibits the mitogenic action of vascular endothelial growth factor and fibroblast growth factor in capillary endothelial cells by blocking Raf activation", *J. Cell Biochem.* 1997; 67:353-366 **[13]** which modulate the release of NO, causing endothelium-dependent vasodilatation. In addition, beta-adrenergic receptors belong to the family of G-protein-coupled receptors and when they are activated by adrenergic catecholamines they can promote a series of intracellular signal transduction pathways as disclosed in Iaccarino G, et al. Ischemic neoangiogenesis enhanced by beta2-adrenergic receptors overexpression: a novel role for the endothelial adrenergic system. *Circ Res* 2005;97:1182-1189 **[12]** and **[13]**. Beta receptor stimulation can induce modifications of signal transduction pathways of angiogenic factors such as VEGF or bFGF as disclosed in **[13]**. It has been demonstrated that the increase of cAMP levels inhibit VEGF- and bFGF-induced endothelial cell proliferation. Pharmacological or beta-adrenergic receptor-mediated elevations in cAMP block mitogen-induced activation of the MAPK signaling pathway leading to blockade of Raf-1 activity via increased PKA activity **[13]**.

[0011] In addition, it has been demonstrated that beta-blockade can induce apoptosis of cultured capillary endothelial cells as disclosed in Sommers Smith S.K. et al, "Beta blockade induces apoptosis in cultured capillary endothelial cells", *In Vitro Cell Dev. Biol. Anim.* 2002; 38: 298-304 **[14]**.

[0012] Despite their benign self-limited course, common IH are rarely responsible during their proliferative phase for local complications such as ulceration or haemorrhage. The so-called alarming IH disclosed for example in Enjolras O. et al. "Management of alarming hemangiomas in infancy: a review of 25 cases", *Pediatrics* 1990; 85:491-8 **[4]** can impair vital or sensorial functions especially when present respectively on upper airways and orbital areas.

[0013] In addition, IH cause at least transient cosmetic disfigurement which trigger psychological morbidity first in parents and later in affected children as disclosed in document **[1]** and in Tanner J.L. et al, "Growing up with a facial hemangioma: parent and child coping and adaptation, Pediatrics", 1998; 101:446-452 **[2]**.

[0014] Systemic or intralesional corticosteroids are used as first line treatments for problematic lesions during the proliferative phase as disclosed in Bennett ML et al, Oral corticosteroid use is effective for cutaneous hemangiomas, An evidence-based evaluation, Arch. Dermatol. 2001; 137 :1208-13 **[3]**.

[0015] However, even at high dosages (2 to 5mg/kg of body weight/day), response rates to treatment range from 30 to 60% as disclosed in documents **[1]**, **[3]** and **[4]**. Adverse effects are usually transient and limited such as cushingoid facies, irritability, growth suppression, but may cause more concern hypertrophic cardiomyopathy.

[0016] Other treatment options include interferon alfa-2a and 2b (40 to 50% of complete response with dosing 1-3 mU/m²/day) (millions of units per m²) but a risk of neurotoxicity has been reported in children under 1 year of age, as disclosed in documents **[1]** and **[5]**; vincristine is also used for its antimitotic properties as disclosed in document **[1]** but its well-known downsides are peripheral neuropathy, constipation, and hematologic toxicity.

[0017] Further, the new anti-angiogenic factors such as avastatin are contra-indicated in young children because of their side effects.

[0018] Moreover, because most patient receiving treatment are infant or small children, patient tolerance for the known compounds becomes of more paramount importance.

[0019] Thus, needs exist of alternative, more efficient and less toxic compounds for the treatment of IH, in particular of infantile capillary haemangiomas. The present invention fulfills these and other needs.

Description of the invention

[0020] Propranolol is a well tolerated non-selective beta blocker commonly used in young children for cardiological indications as disclosed by Villain E et al in Low incidence of cardiac events with beta-blocking therapy in children with long QT syndrome, Eur. Heart J. 2004; 25:1405-11 **[6]**, by Fritz K.I. et al, Effect of beta-blockade on symptomatic dexamethasone-induced hypertrophic obstructive cardiomyopathy in premature infants: three case reports and literature review. J Perinatol 1998;18: 38-44 **[7]**, and by Kilian K. in Hypertension in neonates causes and treatments, J. Perinat Neonatal Nurs. 2003; 17:65-74 **[8]**. But this beta-blocker and beta-blockers in general have never been experimented nor disclosed for a use in the treatment of haemangiomas.

[0021] The present inventors are the first ones to have experimented and observed that beta-blockers may be very efficient to control the growth of IH and even to treat IH. The observations and experimental results are provided in the present application.

vided in the present application.

[0022] Accordingly, in a first aspect, the present invention provides the use of beta blocker for the manufacture of a medicament for the treatment of hemangiomas.

[0023] « Beta blocker » refers also herein to beta-receptor blocking agent, beta adrenergic receptor blocking agent, beta blocking agent, beta-blocking agent or beta-adrenergic receptor blocking agent or any other denomination indicating a chemical that inhibits the binding of agonists, natural or artificial, to beta-adrenergic receptors of any type (beta-1, beta-2, beta-3 or others).

[0024] According to the present invention, the beta blocker may be a non-selective beta blocker, a beta-1-selective beta blocker, a mixture of alpha-1/beta-adrenergic antagonists, a beta-2-selective beta blocker. The beta-blocker may also be a mixture of two or more beta-blockers.

[0025] Preferably, according to the present invention, a non-selective beta blocker is used. It may be selected for example from the group comprising alprenolol, carteolol, levobunolol, mepindolol, metipranolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, timolol or pharmaceutically acceptable salts thereof. A mixture thereof may be used.

[0026] Preferably, the beta blocker is propranolol or a pharmaceutically salt thereof, for example L or D-propranolol or a mixture thereof. The mixture may be a mixture of L and D-propranolol, with an amount thereof of 0:1 to 1:0, for example 1:1. Pharmaceutically acceptable salt of the propranolol may be propranolol chlorhydrate or any other preparation of propranolol, whether or not the preparation changes or alters the pharmacokinetic properties or metabolism of propranolol.

[0027] According to the present invention, the medicament may be a medicament for treating infantile capillary hemangiomas.

[0028] The medicament may be in any form that can be administered to a human or an animal. Administration may be carried out directly, i.e. pure or substantially pure, or after mixing of the beta-blocker with an pharmaceutically acceptable carrier and/or medium. The medicament may be in a form selected from the group comprising an injectable form (for example as Avlocardyl®5mg/ml), syrup (for example as Efferalgan®3%), oral suspension (for example as Efferalgan®3%), a pellet (for example as Dafalgan®1g), powder (for example as Doliprane®100mg), granules (for example as Zoltum®10mg), spray, transdermal patch (for example as Cordipatch®5mg/24h) or local form (cream, lotion, collyrium) (for example as Dermoval creme®, as Betneval®lotion and as Chibroxine® collyre respectively). In these examples, propranolol may be added or may replace the active ingredient(s) of said medicaments.

[0029] The pharmaceutically acceptable carrier may be any know pharmaceutically carrier used for the administration of a beta-blocker to a human or to an animal, depending on the subject. For example, this carrier may be selected from the group comprising for example the

monométhoxy-polyéthylèneglycol (for exemple as in Vi-raferonpeg®) or Liposome (for exemple as in Ambizome®).

[0030] The medium may be any know medium used for the administration of a beta-blocker to a human or to an animal. For example, this medium may be selected from the group comprising for example cremophor (for exemple as in Sandimmun®) or cellulosis (for exemple as in Avlocardyl® LP160mg).

[0031] The pharmaceutical form of the drug is selected with regard to the human or animal to be treated. For example, for a child or a baby, a syrup or an injection is preferred. Administration may be carried out with a weight graduated pipette.

[0032] According to the present invention, the medication may comprise any pharmaceutically acceptable and efficient dose of the beta-blocker to treat hemangiomas. For example, the medicament may comprise a dose allowing an administration of 1 to 5 mg/kg of body weight per day, for example of 2 to 4 mg/kg of body weight/day.

[0033] In a second aspect, the present invention provides a method of treating a subject suffering from hemangiomas is also disclosed. This method comprises the step of administering to said subject a beta-blocker.

[0034] Hemangiomas and beta-blockers, as well as usable formulations are as defined above.

[0035] The administration can be made by using any pharmaceutical way known by the skilled person and useful to administrate a beta-blocker. Examples of administrable forms of medicament are provided above. For example, the administration can be made by direct injection of the beta-blocker. This way of administration, as well as a syrup, is of course preferred for babies.

[0036] The administration may be defined so as to allow delivery of a pharmaceutically acceptable and efficient dose for the treatment of hemangiomas. For example, the administration may comprise a dose of 1 to 5 mg/kg of body weight per day, for example of 2 to 4 mg/kg of body weight/day. The administration may be carried out with one dose or with a plurality of doses per day.

[0037] The inventors of the present application demonstrate clearly experimentally a strong anti-angiogenic effect in infantile capillary hemangiomas (IH) by the use of a beta-blocker.

[0038] Since the new anti-angiogenic factors of the prior art such as avastatin are contra-indicated in young children because of their side effect, the use of propranolol according to the present invention constitutes a safe alternative to systemic corticosteroids, and even to interferon or vincristine.

[0039] Propranolol is a non-selective beta-blocker with weak intrinsic sympathomimetic activity, and its dramatic therapeutic effect on IH could be explained by three mechanisms:

1. a peripheral vasoconstrictor effect inducing cell hypoxia, Propranolol is responsible for peripheral va-

soconstriction, and this effect is immediately visible on the IH we have treated.

2. a decreased expression of VEGF and bFGF genes via the down regulation of the Raf/MAPK pathway, or
3. an apoptosis triggering effect on capillary endothelial cells.

[0040] In the experimental results disclosed hereunder, a change in color from intense red to purple, associated with a palpable softening of the lesion was observed on babies presented with an IH. This effect could induce a chronic hypoxia of the hemangioma responsible for an arrest of endothelial cell proliferation.

[0041] However, in inventor's experimentations, the progressive improvement of IH under propranolol treatment suggests strongly a sustained action on proliferative growth factors.

[0042] It is not clear whether in this respect the targets of the treatment are the endothelial cells themselves, or other cells such as interstitial cells or mast cells. The third mechanism possibly involved to explain the involution of IH is an early endothelial cell apoptosis induced by the beta blockade.

[0043] However the re-growth of the hemangioma in two of the presented cases, when the treatment was stopped during the proliferative phase of the IH, does not support this hypothesis. In addition, in the second case the inventors did not find apoptotic cell markers by immuno-histochemistry using antibodies to cleaved caspases 3 and 8.

[0044] Further, the use of beta-blockers is now widespread in neonate or children patients with a good tolerance in cardiac diseases as long QT syndrome as shown in document Villain E. et al, "Low incidence of cardiac events with beta-blocking therapy in children with long QT syndrome", Eur. Heart J. 2004; 25:1405-1411 **[6]**, hypertrophic cardiomyopathie as shown in document Fritz K.I. et al, "Effect of beta-blockade on symptomatic dexamethasone-induced hypertrophic obstructive cardiomyopathy in premature infants: three case reports and literature review", J. Perinatal 1998; 18:38-44 **[7]** or hypertension as shown in document Kilian K. et al, "Hypertension in neonates causes and treatments", J. Perinat. Neonatal Nurs 2003; 17: 65-74 **[8]**.

[0045] This invention is further illustrated by the following examples with regard to the annexed drawings that should not be construed as limiting.

Brief description of the drawings

[0046]

- Figure 1 is a picture showing the aspect of a hemangioma after 4 weeks of a prior systemic steroids treatment, before beginning of propranolol treatment.
- Figure 2 is a picture showing the aspect of the hemangioma only seven days after onset of propranolol treatment according to the present invention.

- Figure 3 is a picture showing experimental results at 6 months of age where the child still continues to be treated according to the present invention and prior systemic steroids treatment was stopped since 2 months.
- Figure 4 is a picture showing the experimental results at 9 months of propranolol treatment according to the present invention.

EXAMPLES

Example 1 : first experiments according to the present invention

[0047] A male baby presented with an IH involving the nasal pyramid. At 2 months of age, systemic steroids were introduced because of dyspnea associated with nasal partition and columella necrosis. After a one-month treatment at 3 mg/kg of body weight/day (mg/kg/day) of prednisolone, the hemangioma was stabilized, but nasal necrosis progressed. Since the infant progressively refused to take prednisolone tablets, we introduced an equivalent dosage of bethamethasone in drops (0,5mg/kg/day). At 4 months of age, the hemangioma had stopped growing and intra nasal ulcerations had healed.

[0048] However, the child returned at a control visit with tachycardia at 180 to 200 pulses per minute, associated with a systolic cardiac murmur. A cardiac sonography showed an obstructive hypertrophic myocardiopathy, justifying a decrease of the betamethasone dosage from 3 to 2 mg/kg of body weight /day (mg/kg/day).

[0049] We have thus initiated a treatment with a beta-blocker, propranolol (chemical IUPAC name: (2RS)-1-[1-methylethyl)amino]-3(naphtalen-1-yloxy)propan-2-ol) at 3 mg/kg/day. Propranolol was administered as a capsule containing commercial propranolol powder. The day after the onset of propranolol treatment the hemangioma changed in color from intense red to purple, and softened. Betamethasone was replaced by prednisolone which was progressively tapered down and stopped 6 weeks after initiation of propranolol.

[0050] Despite the decrease of systemic steroids, the IH still continued to improve. At age 5 months $\frac{1}{2}$, when steroids had been stopped, no rebound in size or coloration of the IH could be noted. At 14 months of age, the child was still under propranolol, and the corticosteroid-induced hypertrophic cardiomyopathy had regressed. The IH was completely flat, with the persistence of only skin telangiectasias on a yellow-orange discolored skin background, and sequels of intranasal and columella necrosis.

Example 2 : second experiment according to the present invention

[0051] The second infant, a male triplet, born at 30 weeks, presented since birth a plaque-like IH involving

the entire right upper limb and the right fronto-parietal and superior eyelid areas.

[0052] At one month of age a subcutaneous component developed in 3 areas including the superior eyelid, the parotid region and the axillary fold. Because of risk of visual deprivation prednisolone was started at 3 mg/kg/day.

[0053] However, after 2 weeks of treatment the situation was not under control and we decided to increase prednisolone at 5 mg/kg/day for 2 weeks.

[0054] Despite this regimen the IH continued to enlarge and at 2 months of age eyelid opening was impossible, the right side of the face being deformed by an enormous tumor as shown in annexed figure 1. In addition the axillary fold was occupied by a tumoral IH component measuring clinically 5 cm in diameter.

[0055] MRI showed no intra-cerebral anomalies, but revealed that the IH involved extra and intraconal orbital areas and was responsible for exophthalmia. In addition, MRI showed that the parotid IH was in continuity with a compressive intra-cervical component leading to tracheal and oesophageal deviation; the axillary mass measured 26mm x 45mm x 40mm and extended to the right pulmonary apex.

[0056] A cardiac sonography showed an increased cardiac output.

[0057] The dosage of prednisolone was reduced to 3 mg/kg/day and a treatment with Propranolol, 2 mg/kg/day, according to the present invention, was initiated.

[0058] Like in the previous infant (see above example 1), the lesions softened only 12 hours after the onset of propranolol.

[0059] Seven days after, spontaneous ocular opening was possible due to a dramatic reduction in size of the subcutaneous component of the hemangioma as shown in the picture presented in annexed figure 2. Parotid and axillary masses were considerably reduced in size.

[0060] These unexpected results obtained with the present invention have to be compared with those presented in the picture of annexed figure 1 that shows the aspect of the hemangioma before onset of propranolol treatment and after 4 weeks of a prior art systemic steroids treatment (2 weeks at 3 mg/kg/d and 2 weeks at 5 mg/kg/d).

[0061] Prednisolone treatment was progressively tapered down while the IH continued to improve. At 3 months of age a biopsy sample was obtained on the arm, showing a typical IH. Endothelial cells demonstrated poor staining with the monoclonal antibody MIB-1 suggesting a weak proliferative activity for an IH in a young infant.

[0062] In order to assess a possible proapoptotic role of propranolol, immuno-histochemical analysis using monoclonal anti-cleaved caspase-3 and 8 antibodies (Ozyme, Saint Quentin en Yvelines, France), was performed but did not demonstrate positive immunostaining [15].

[0063] Prednisolone was stopped at 4 months of age,

without any rebound, but a 3-day interruption of propranolol treatment was responsible for a mild increase in size of the hemangioma on the superior eyelid and parotidal areas.

[0064] Reintroduction of propranolol treatment at 2mg/kg/day was successful after only 24 hours.

[0065] At 6 months of age, the eye opening was satisfactory and no major visual impairment was noted, the parotidal and axillary subcutaneous hemangiomatous components were not palpable and the IH had considerably faded on both face and arm.

[0066] Figure 3 provides a picture showing these experimental results at 6 months of age where the child still continue to take 2 mg/kg/d of propranolol but systemic steroids were stopped since 2 months. No subcutaneous component of the hemangioma was noted, and the cutaneous component had considerably faded. In addition the child does not suffered of any visual impairment.

[0067] At 9 months of age, the treatment was stopped, without any re-growth of the IH as shown in the picture of annexed figure 4.

Example 3: third experimentation according to the present invention

[0068] A baby girl presented with a right periocular IH noted first at 3 weeks of age and localized on the internal canthus. At 2 months of age, the subcutaneous component of the IH extended into the orbit and limited the opening of the superior eyelid.

[0069] Doppler ultrasonography showed an IH measuring 32mm in diameter and 12mm in thickness.

[0070] After informed consent obtained from the parents, she was treated with propranolol 2 mg/kg/day. Flattening of the lesion was noted in 12 hours, followed by a progressive improvement.

[0071] Control ultrasonography, performed 7 days after the onset of propranolol, showed a decrease in size of the IH : 21mm in diameter versus 32mm and 6mm in thickness versus 12mm, without any hemodynamic modifications.

[0072] Propranolol was stopped after one month, but a novel increase in size of the IH was noted, necessitating the treatment to be resumed.

[0073] At 7 months of age the IH was flat and had faded in color, and ultrasonography could not identify any subcutaneous component.

[0074] Propranolol was stopped at 8 months without any rebound of the hemangioma.

[0075] Seven other child suffering from hemangiomas have been treated with propranolol and similar results were obtained. No treatment failure has been observed with the present invention. This kind of results were never achieved in the prior art, for example with corticotherapy or interferon.

[0076] In summary, these examples show clearly that propranolol has a strong anti-angiogenic effect in IH. Since the new anti-angiogenic factors such as avastatin

are contra-indicated in young children because of their side effects, propranolol, may constitute a reasonable safe alternative to systemic corticosteroids, and even to interferon or vincristine.

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[0077]

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Claims

1. Use of beta blocker for the manufacture of a medicament for the treatment of hemangiomas. 20
2. The use according to claim 1, wherein the beta blocker is a non-selective beta blocker.
3. The use according to claim 1 or 2, wherein said beta blocker is selected from the group comprising alprenolol, carteolol, levobunolol, mepindolol, metipranolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, timolol, or pharmaceutically acceptable salts thereof. 25
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4. The use according to claim 1 or 2, wherein said beta blocker is propranolol or a pharmaceutical salt thereof. 35
5. The use according to anyone of claims 1-3, wherein the medicament is a medicament for treating capillary hemangiomas and/or capillary infantile hemangiomas. 40
6. The use of anyone of claims 1-5, wherein the medicament is a syrup or an injectable solution. 45
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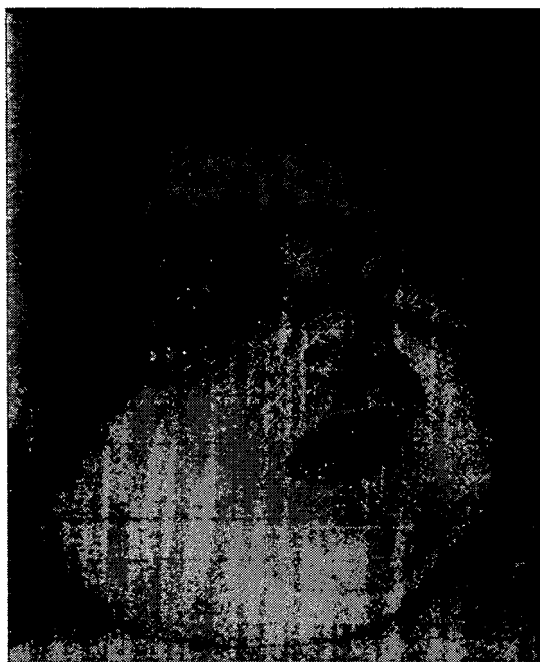


FIGURE 1



FIGURE 2

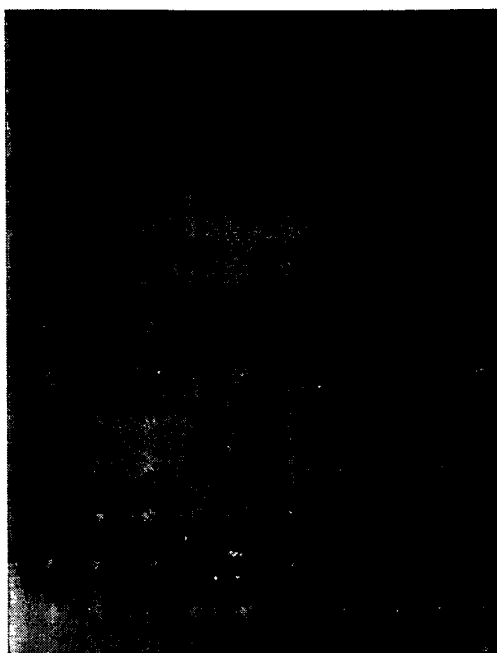


FIGURE 3

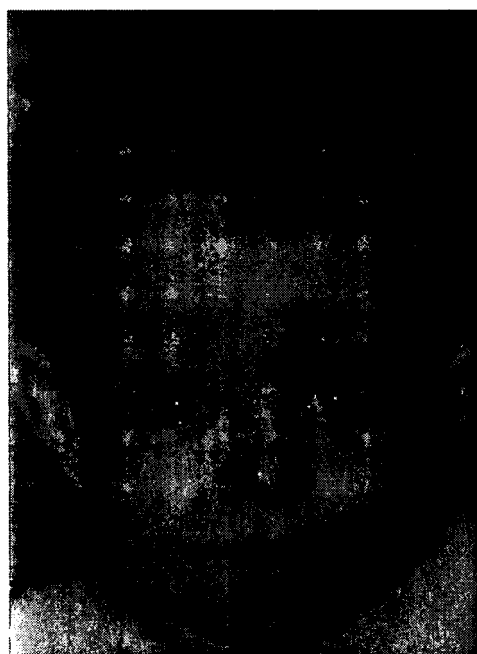


FIGURE 4



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 07 29 1273

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
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			A61K
The present search report has been drawn up for all claims			
Place of search		Date of completion of the search	Examiner
The Hague		17 March 2008	Cielen, Elsie
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

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EPO FORM 1503 03.82 (F04C01)



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EUROPEAN SEARCH REPORT

Application Number
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